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Jatropha dioica, an Aztec plant with promising pharmacological properties: A systematic review

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Few pharmacological and toxicological studies have been conducted to demonstrate the usefulness and safety of using the *Jatropha dioica* extract. The aim of this study was to update the state of the art on the chemical composition, pharmacology, and toxicology of the species *J. dioica*, to find new possible applications. A search of different databases was carried out on the internet, specifically in Science Direct, PubMed, EBSCO, SCOPUS, Web of Science and Springer Link, with the keyword being "*Jatropha dioica*". Despite the limited results with regard to the plant toxicity, it was shown that the extract to use is innocuous. In addition, it was found that *J. dioica* could be employed as an antioxidant, antibiotic, antifungal, or antiviral agent. Although promising, more scientific research is needed to further validate the ethno pharmacological use of the *J. dioica* extracts.

Key words: *Jatropha,* toxicity, chemical composition, ethno pharmacology, plants medicinal.

INTRODUCTION

The great biodiversity of medicinal plants in Mexico is an important source of remedies with an enormous cultural

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acceptance (Cirilo Aguilar et al., 2011). Although the use of medicinal plants was neglected for a long time, there is currently a great interest in their study due to their great therapeutic potential. That interest is focused today, essentially, on the pharmacological benefits derived from the consumption of the extracts from the fruits, seeds, vegetables, barks and roots. However, the lack of medicines and the adverse effects of many of them have made the use of medicinal plants and their extracts to play an important role for the treatment of ailments such as diabetes and cancer (Kim et al., 2013). Large number of plants belonging to the Euphorbiaceae family have been shown to have a number of medicinal benefits, industrial utility and applications in food (Sharma and Singh, 2012). Some authors have reported on the use of *Jatropha* species to produce biodiesel (Fresnedo-Ramírez and Orozco-Ramírez, 2013). In addition, it was reported that this species has important effects anticonvulsants, anticancer, hypoglycemic, hypotensive, anti-inflammatory, antimicrobial, and antioxidant (Kumar et al., 2016; Sharma and Singh, 2012).

Jatropha dioica Cerv. is a species of *Jatropha* with a succulent shrub, originally from Mexico but can also be found in Texas and Arizona (Aggie, 2010). The species is known for unusual names as "blood of the dragon", "sangre de drago" (Govea-Salas et al., 2017), "Tlapelex Ptali" by the Aztecs (Dominguez et al., 1980) or "Sangregado". The color appellative is due to the sap juice change the color when exposed to air from colorless to dark red. Its branches are reddish-brown with dark green leaves that are narrow in appearance. Its flowering period falls between April and May (Martinez et al., 2014).

Research of *J. dioica* can result in finding new bioactive compounds and provide new phytopharmaceutical drugs that can be used as therapeutic alternatives in some illness (Chandran et al., 2016). However, there is a little information available about the chemical composition, pharmacology and toxicology of this plant species.

The objective of this research was to update the state of the art on the chemical composition, pharmacology, and toxicology of the species *J. dioica*, to find new possible applications.

MATERIALS AND METHODS

Data acquisition

A search was carried out on different databases with Pub-Med, Web of Science, Science Direct, EBSCO, Scopus and Springer link using the descriptor "*Jatropha dioica*". The literature search was carried out in English and Spanish from 1978 to 2018.

Final selection of the information

The search was performed concerning studies that were carried out on the plant *J. dioica*, selecting all those works that involved this plant in the investigation (Figure 1).

Data extraction

The selected articles were analyzed in order to systematize and facilitate the understanding of this plant studies. No article was rejected on the bases of methodological reasons.

RESULTS AND DISCUSSION

Publication related to *J. dioica*

Figure 2 shows the number of publication related to *J. dioica* found on the different databases. In SCOPUS, just nine articles were found. In Science Direct three research papers were found, repeats of the previous database. While in PubMed four works were obtained, all were repeats of the previous database. In EBSCO search there were two works that were already reported in the previous databases. In the Web of Science, nine works were obtained, where only two were new finds. In Springer link no article was found related to *J. dioica* in the title, giving a total of 11 works that involved the appearance of *J. dioica* in the title.

Figure 2 also shows the trend of publication about *J. dioica* from 1970 to 2018. Among them are just few studies related to composition, pharmacology, and toxicology of *J. dioica.*. From 1970 to 2010, 2 publications were found; however, from to 2011 to 2018, the number of investigations increased up to 09. The increase in the number of publications is most likely due to the need for finding new sources of highly effective, economic, and harmless medications. This sudden jump in the number of publications demonstrates that *J. dioica* is a plant of rising interest, though not much studied by Mexican and world researchers (UNAM, 2010; Wong-Paz et al., 2010).

Botanical aspects

The botanical description of *J. dioica* (Figure 3) is: Kingdom: Plantae; Clade: Magnoliophyta; class: Magnoliopsida; Order: Malpighiales; Family: Euphorbiaceae; Subfamily: Crotonoideae; Tribe: Jatropheae; Genus: *Jatropha*; Species: *dioica* (UNAM, 2010). This species inhabits areas with a dry and semi-dry clime, such as the territory of Texas, USA and the Northern Mexico, even though it can be found throughout the Mexican territory (Flores-Torres et al., 2019; Gutiérrez et al., 2018). *J. dioica* is a shrub of 50 to 150 cm in height, reddish-brown branches with narrow, long, and dark green leaves. The flowers are grouped in cymes, the male flowers are small while females are bigger, with a light pink color (UNAM, 2010).

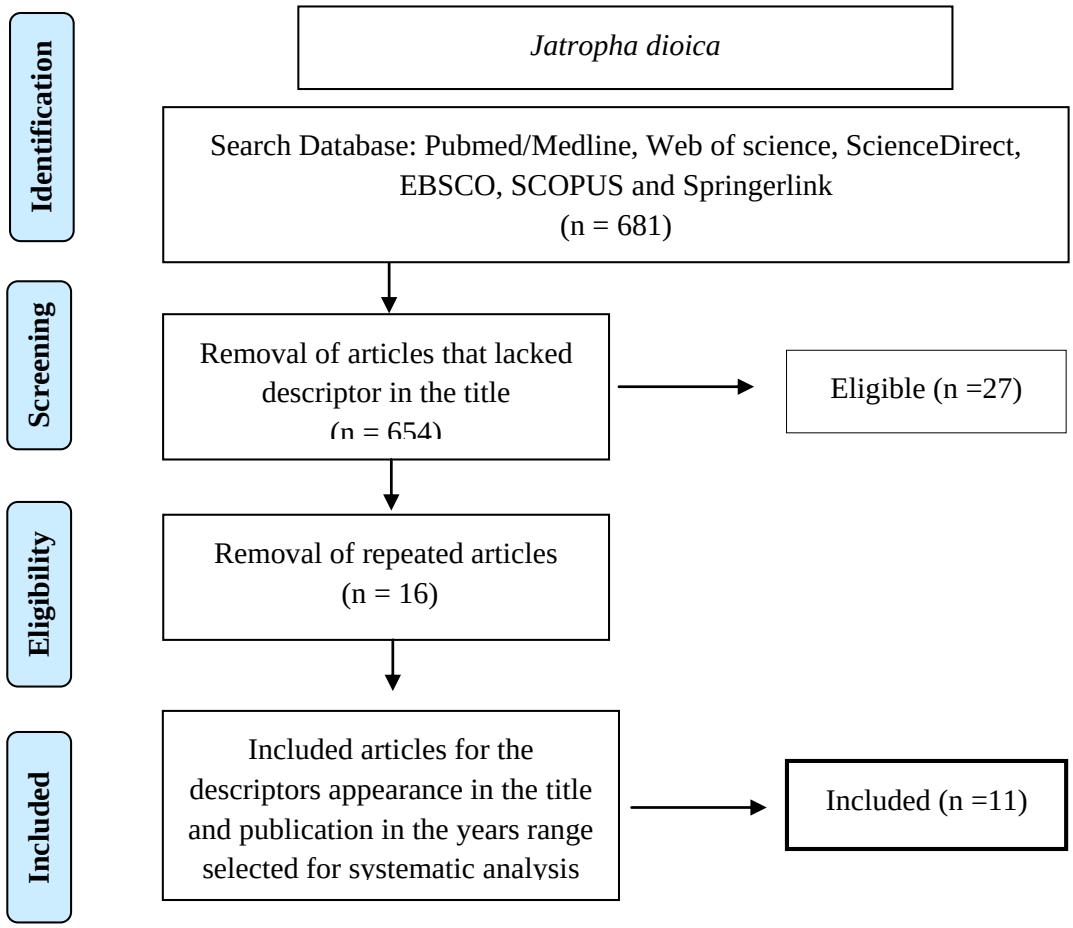

Figure 1. Flow diagram of the selection criteria for articles of interest.

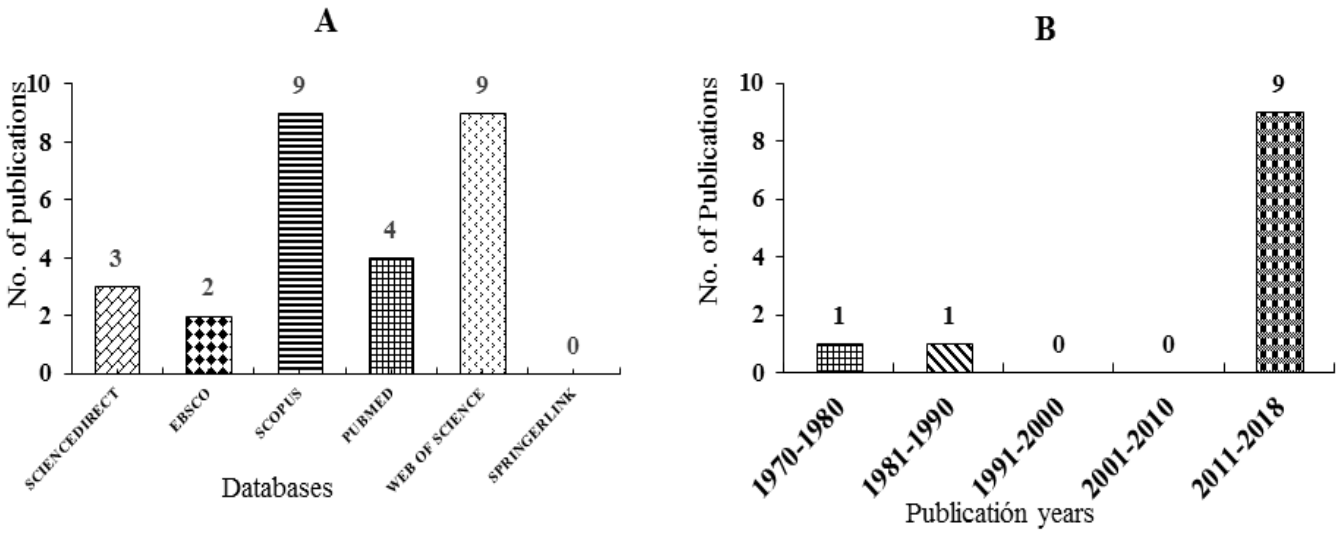

Figure 2. The number of publications over the last 40 years related to *J. dioica* plant family and publications of research related to the plant *J. dioica* found in different databases. A: Search of articles that contain descriptor in the title. B: Articles that contain descriptor in the title selected for this systematic analysis by decade.

Figure 3. Pictures of the plant *Jatropha dioica* (dragon blood) taken in May 2017 near spring El Ejido, Matamoros municipality, Coahuila, Mexico. Latitude: 25.529287 | Length: -103.231997

The plants bloom in spring and early summer. The fruits are globose with seeds inside (Eggli, 2001; Valenzuela Soto, 2014).

Traditional usage of *J. dioica*

From a medical stand point, the use of *J. dioica* is diverse and has been attributed to each of the parts that make up this plant. Endemic to Mexico, this plant is known by different names throughout the country: batacora (Baja California), coatli and dexthi (Hidalgo), drago, felondilla and gualulo (Hidalgo), matacora (Baja California), piñon de cerro, sangre de drago (Hidalgo, Valle de Mexico), sangre de grado (Durango, Valle de Mexico), sangre gaco, sangregada and sangregado (Coahuila, Durango, Sinaloa, Sonora), sangregrado (Durango, San Luis Potosi, Sonora, Zacatecas), sangregrao and suzi (Oaxaca), tacote prieto (Sinaloa, Sonora), telondilla (Ciudad de Mexico, Hidalgo), tlapalezapatli (Nahuatl), torote amarillo and torote prieto (Baja California) (Manzanero-Medina et al., 2009).

The root is macerated or boiled in order to extract a liquid which is then used to rinse the hair and slow hair loss (Razo Rodríguez and Alvarado Bárcenas, 2014). Similarly, once boiled, the resulting liquid can be used as bath water to cleanse wound infections (Wong-Paz et al., 2010), weakness, kidney pains and problems with absorption (Manzanero-Medina et al., 2009). In order to treat these illnesses, a fistful of roots should be boiled in approximately three or four liters of water (Castillo et al., 2010). Due to its high tannin content, it is used as a dye, a preservative and mainly to tan animal skins (Castillo et al., 2010). It also functions as an antibiotic. It treats periodontist, and also alleviates pain when the roots or stalk are chewed. It reduces inflammation of the venous and respiratory passages (ulcers and hemorrhoids), cures acne and other skin allergies and treats dandruff and itching (Bravo Luna et al., 2000) in addition to healing wounds (Ocegueda, 2005).

The stalk is utilized in the treatment of colon, prostate, cervical, tongue, stomach and skin cancers in their early stages (Martínez et al., 2014). Drops of liquid extracted from the stalk are then mixed in a liter of water and taken daily (Barba Avila et al., 2003). It is also used against ascorbic acid deficiency (Oropeza Dominguez, 2006).

The leaf and seeds are consumed as laxatives (Can-Aké et al., 2004). It is also said to be useful in the treatment of sore eyes, the elimination of cloudiness of vision and blindness. To do so, the fruit is squeezed, thereby allowing a few drops to fall directly into the eye (Arturo et al., 1994). It has also been reportedly used against scleral diseases (Valenzuela Soto, 2014). Oil extracted from the seeds is used to treat oral blisters, eczema and itchiness. This oil contains phenolic components, which promote biological antifungal activity (Pabón and Hernández-Rodríguez, 2012).

Antimicrobial and antifungal activity

The extracts of *J. dioica* has shown different antimicrobial activity depending on the solvent used in the preparation and the part of the plant used. Root extract made with hexanol was more potent than extracts made with alcohol and acetone. These extracts were evaluated in human pathogens such as *Bacillus cereus, Escherichia coli, Salmonella* Typhi*, Staphylococcus aureus, Enterobacter aerogenes, Enterobacter cloacae, Salmonella typhimurium, Cryptococcus neoformans, Candida albicans, Candida parapsilosis,* and *Sorothrix schenckii.* This high antibacterial and antifungal activity may come from the presence of β-sitosterol (terpene) compounds in the plant (Silva-Belmares et al., 2014).

Soxhlet extracts of roots prepared with different solvent concentration were evaluated against *S. aureus*, *E. coli*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Streptococcus mutans* (strands 35531 and 31377), and *Klebsiella pneumoniae* (strands 042, 88142, 17-2, 88145, and 49766) (Escareño-Piña, 2017; Terrazas-Hernández et al., 2018). Hexane extract showed the best inhibitory behavior with the lowest minimum inhibitory concentration against *S. mutans* and *Klebsiella pneumoniae*. In other studies, methanol extracts were assessed for the activity against *S. aureus* and *K. pneumonia* (Dominguez et al., 1980; Serrano-Gallardo et al., 2017). Studies indicate that the hydro-alcoholic extracts of the root has an activity against *C. albicans* (Alanís-Garza et al., 2007), which was confirmed by others (Oliveira Simone et al., 2013) who also determined the minimum inhibitory concentration and minimum fungicidal concentration leaves and roots extracts. This plant has been used as tooth strengthening remedy, thus the ethanoic root extracts (Terrazas-Hernández et al., 2018) and aqueous plant extracts (Vargas-Segura et al., 2018) were recently evaluated against *S. mutans* and the minimum inhibitory concentration and half maximal inhibitory concentration were determined to be 2 mg/mL and 250 ppm, respectively.

Antiviral effect

Silva-Mares et al. (2013) reported that *J. dioica* root hydro-methanolic extract showed antiviral activity against herpes type 1 and type 2 (HSV-1 and HSV-2, respectively). The fractions of hexane were analyzed chromatographically, indicating the presence of metabolite diterpene (riolozatrione) as the main compound. The authors also mentioned that the extract displayed slight cytotoxicity.

Hypoglycemic effect

Within the family Euphorbiaceae, the genus *Jatropha* has been considered as a therapeutic alternative for the treatment of diabetes mellitus (DM) (Aladodo et al., 2013; Kumar et al., 2016). Other studies show the hypoglycemic effect of the phenolic fraction and ethanolic extract isolated from leaves of *Jatropha aethiopica*. The authors deduced that the ethanolic extract as the phenolic fraction contributes to the improvement of glucose tolerance, but the ethanolic extract exhibited a relatively greater effect compared to a biguanide such as metformin (Gamiotea-Turro et al., 2018).

The study by Rahuja et al. (2013) evaluated *Jatropha gossypifolia L.* extracts against type 2 diabetes mellitus.

They found a significant lowering of blood glucose level in DM-induced rats. The authors suggested that the extracts probably have insulin secretaceous activity related to inhibitory activity for α-glucosidase, enzyme hydrolase, essential for the catabolism of glycogen to glucose in the lysosomes, thus reducing the absorption of carbohydrates from the digestive tract, which can stop the release of D-glucose, thus reducing the plasma glucose levels (Sevilla-Asencio et al., 2013). Another study by Granados et al. (2015) showed an improvement in glucose absorption and tolerance on two cell models (Myotubes C2C12 and adipocytes 3T3-L1), with exposure to extracts of *J. gossypifolia* for 4 h, *in vivo.*

Hypoglycemic activity has been attributed to extracts of *Jatropha curcas* leaves showing improvement of changes in lipid metabolism in DM alloxan induced rats, significantly reducing glucose levels, more so at a higher dose (Patil et al., 2011), which could be attributed to the presence of specifically expressed sequence tags in that plant (Sahu et al., 2014). *J. dioica* also has shown to have hypoglycemic activity (Alarcon et al., 1998).

Antioxidant activity and genoprotector effect of *J. dioica*

The presence of terpenoids compounds, flavonoids, reducing sugars and alkaloids are possibly responsible for the antioxidant effect observed using model radical scavenger (1, 1-diphenyl-2-picrylhydrazyl, DPPH) for the root extracts of *J. dioica* (Wong-Paz et al., 2014). Similarly, the plant extracts show a genoprotector effect on mouse liver, renal and bone marrow cells evaluated with comet assay (Martínez et al., 2014; Ramírez-Moreno et al.). Using root extract of *J. dioica* showed that antioxidant activity is directly proportional to the amount of polyphenols in hydro-alcoholic (Ramírez et al., 2016).

The antioxidant capacity was demonstrated using a radical scavenger's DPPH and radical cation scavenger (2,2-azino-bis 3 ethyl benzothiazoline-6- sulfonic acid) ABTS relating it to the presence of phenolic compounds in the plant (Wong-Paz et al., 2015). Studies looked at the sterilization effect on the extracts of *J. dioica* root (Terrazas-Hernández et al., 2018). They reported that even though the high temperatures of sterilization increased total phenolic content (TPC) and changed the color of the solution (Maillard reactions), it did not influence its antioxidant activity (DPPH and ABTS arrays) or antibacterial behavior against *S. mutans*. TPC also depends on the climate condition and extraction method (Gutiérrez-Tlahque et al., 2018), with winter drought, UV exposure, and solvent composition higher in alcohol increasing the concentration and antioxidant activity. Similarly, solvent composition (% alcohol) and extraction method (heat reflux vs. ultrasound-assisted) can strongly influence the amount of TPC in the plant extract (Wong-Paz et al., 2014).

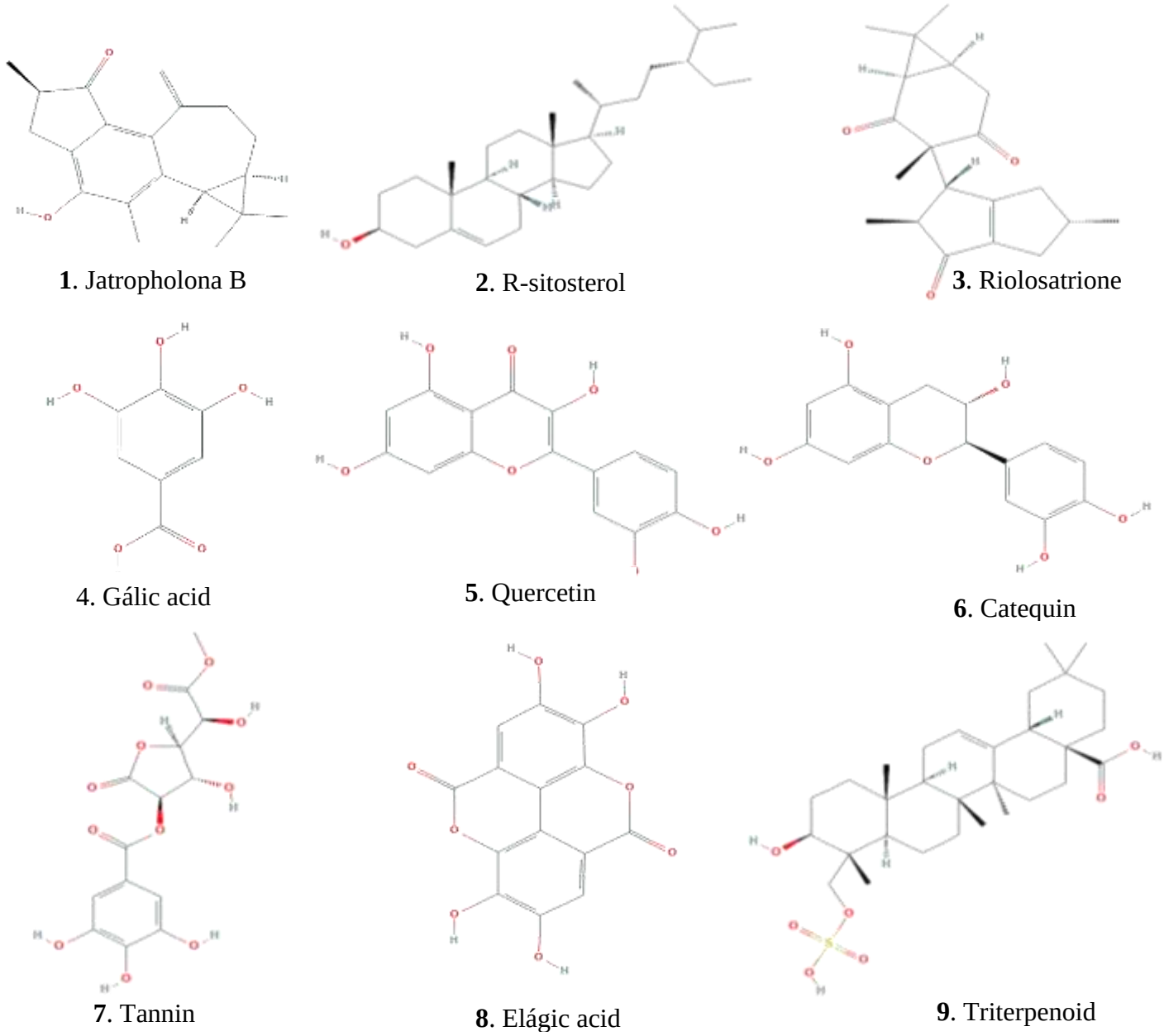

Figure 4. Chemical structure of the compounds reported in *J. dioica*. Source: Pub chem (https://pubchem.ncbi.nlm.nih.gov).

Chemical composition

Some ethnobotanical uses may be attributed to the presence of secondary metabolites such as polyphenols (Aguilera-Carbo et al., 2008). The studies carried out in *J. dioica* have identified characteristic chemicals such as steroid alcohols (Burgueño-Tapia et al., 2017), flavonoids, tannins (Mendoza-Moreno, 2000), and terpenes, among others (Perroni et al., 2014). Figure 4 shows the chemical structure of the compounds reported in *J. dioica*. Overall, this plant is a good candidate to obtain nutraceutical and functional ingredients due to the amount of polyphenols present (Wong-Paz et al., 2014).

Cytotoxicity

The extracts of *J. dioica* do not show toxicity or low cytotoxicity at concentrations used in literature. Studies carried out in micronuclei of peripheral blood of mouse

Table 1. Pharmacological activity of *J. dioica*.

Group	Compound	Activity	Reference
Sterols	Jatropholona B	Antitumor effect, gastroprotective activity.	Melchor-Martínez et al. (2017), Pertino et al. (2006)
	R-sitosterol	Chemo-protective activity against colon cancer, using in vitro and in vivo models.	Baskar et al. (2010).
	Citlalitrione	Antiviral and antitumor effect	Dominguez et al. (1980), Melchor-Martínez et al. (2017)
	Riolosatrione	Its bioactivity has not been evaluated	
	Triterpenes	Antibiotic activity against *Staphylococcus aureus.*	Chen et al. (1994)
Flavonoids	Quercetin	Protects against glucotoxicity preventing the aggregation and functional loss of proteins. Antimicrobial activity against fungi and bacteria: G*ram-positive* and *Gram-negative.*	Civelek et al. (2019), Sati et al. (2019)
	Catechin	Regulates the bioavailability of nitric oxide, improving endothelial function among people with high blood pressure, diabetes, and heart disease	Galleano et al. (2010)
Polyphenols	Tannins	Antitumor and antibacterial activity, a strong inhibitor of *E. coli*.	Chen et al. (1994)
Phenols	Ellagic acid	Antioxidant, antimicrobial, and antiparasitic properties. Antitumor effect by inhibiting the mutation of healthy cells in bladder preventing cancer.	Ascacio-Valdés et al. (2013)
	Gallic acid	Antioxidant activity and antibacterial effect against *E-coli*.	Baquero and Gordillo (2013)

(strain BALB-C) using the aqueous extract of root of *J. dioica* showed no cytotoxic effect nor genotoxic (Araujo-Espino et al., 2017). Similarly, aqueous and ethanol extracts from leaves and roots showed low cytotoxicity in 3T3/NIH mouse fibroblasts measured photometrically in a 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide assay after a 24 h exposure (Oliveira Simone et al., 2013).

Other properties of *J. dioica*

According to the digital library of traditional Mexican medicine (UNAM, 2010), this plant has many traditional medicinal uses. There are reports of an ancestral use by the Kickapoo Indians, who used the latex of *J. dioica* to relieve liquid or frequent bowel movements, and to remove thorns from the skin (Latorre et al., 1977). An interesting report (González and González-Chávez, 2006) indicates that *J. dioica* has the ability to accumulate zinc, cadmium, and nickel from mining-polluted soils. Recently, aqueous *J. dioica* extract was used as a reducing agent in synthesis if zinc oxide nanoparticles (Villanueva-Ibáñez et al., 2018), however, the authors did not dwell on the function of the extract's composition. Table 1 shows the pharmacological activity of *J. dioica.*

CONCLUSIONS AND FUTURE OUTLOOK

Despite being a plant native to Mexico, there are few scientific reports on the medical and nutritional properties attributed to this plant. The antioxidant capacity of this plant has been mostly investigated, however, there is still insufficient analysis of these. The extracts of *J. dioica* were found to be used as a protector or antioxidant, yet there is no literature report of human studies. There is not enough systematic evidence to ensure that the ethnobotanical use of this plant is safe. With an increase in interest in this plant, the focus should be in the application of *J. dioica* extracts in the field of phytopharmacology specifically in studies focused on the treatment of diabetes, gums, and gastric ulcers. Further research is required of the plant and the identification of its active constituents, since there is unsatisfactory analysis of the composition and structure of the metabolites present in the plant.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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